PROPHYLACTIC INTRAVENOUS ADMINISTRATION OF STANDARD IMMUNE GLOBULIN AS COMPARED WITH CORE-LIPOPOLYSACCHARIDE IMMUNE GLOBULIN IN PATIENTS AT HIGH RISK OF POSTSURGICAL INFECTION

THE INTRAVENOUS IMMUNOGLOBULIN COLLABORATIVE STUDY GROUP*

Abstract *Background.* Infections and their sequelae are a major cause of death among patients admitted to the surgical intensive care unit (ICU). Studies of passive immunotherapy with standard intravenous immune globulin and hyperimmune globulin directed against gram-negative core lipopolysaccharide to prevent gram-negative infections and their serious systemic complications have had equivocal results in such patients.

Methods. We performed a double-blind study to assess the efficacy of standard immune globulin and core-lipopolysaccharide hyperimmune globulin in preventing infections in surgical patients at high risk. The patients received standard immune globulin (400 mg per kilogram of body weight), hyperimmune globulin (400 mg per kilogram), or placebo (25 percent albumin, 8 ml per kilogram) weekly, for a maximum of four doses while in the ICU.

Results. A total of 352 patients were enrolled, and 329 could be evaluated. The number of patients in whom infections developed was significantly lower in the group receiving standard immune globulin than in the placebo group (36 of 109 vs. 53 of 112 patients, P = 0.03), as was the incidence of pneumonia (15 vs. 30 cases, P = 0.04), especially pneumonia due to gram-negative bacteria (5 vs. 16 cases, P = 0.02). The number of days spent in the ICU and the total days spent in the hospital were lower in the standard immune globulin group (medians of 2 and 7.5 days fewer; P = 0.02 and 0.06, respectively). In contrast, the hyperimmune globulin had no detectable prophylactic effect on infections (50 of 108 patients, with 25 cases of pneumonia). The rate of systemic infections and shock was similar in the three study groups, and hospital mortality did not differ significantly among them.

Conclusions. Intravenous immune globulin given prophylactically to selected high-risk patients in the surgical ICU can reduce the incidence of infection. Core-lipopolysaccharide hyperimmune globulin is not effective in preventing gram-negative infections and their systemic complications. (N Engl J Med 1992;327:234-40.)

INFECTIONS remain the leading cause of death among patients admitted to the surgical intensive care unit (ICU) despite improvements in supportive care and the development of new broad-spectrum antibiotics. Adjunctive therapeutic measures are needed to prevent infections in this setting. Data from studies of other groups of immunocompromised patients imply that standard intravenous immune globulin can prevent bacterial infections,[1-3] but studies of patients who have undergone high-risk surgery have been inconclusive.[4] Infections due to gram-negative bacteria are both frequent and difficult to treat, and the mortality among patients with gram-negative bacteremia is 20 to 40 percent.[5-7] Among patients with septic shock, the currently reported mortality is about 50 percent.[7-11] The poor outcome of such infections is attributed to the effects of gram-negative bacterial endotoxin, a lipopolysaccharide of the outer bacterial membrane. The outer side chains of lipopolysaccharide are responsible for antigenic specificity (O antigens), whereas the inner core region, including lipid A, is a more conserved structure and is primarily responsible for the biologic effects of lipopolysaccharide. The core region of lipopolysaccharide is exposed at the surface of rough mutants of gram-negative organisms, which are devoid of side chains. Clinical studies have suggested that treatment with antiserum obtained from volunteers immunized with the rough mutant *Escherichia coli* J5 could reduce the number of deaths due to gram-negative bacteremia[12] and could prevent gram-negative septic shock when administered prophylactically to high-risk surgical patients.[13]

A preparation of intravenous immune globulins containing high titers of antibodies to core lipopolysaccharide (core-lipopolysaccharide immune globulin) was derived from the plasma of donors screened for naturally occurring high levels of antibodies to the lipopolysaccharide of one of the rough mutants, the R595 strain of *Salmonella minnesota.* Preliminary findings suggested that antibodies directed against R595 lipopolysaccharide could prevent the biologic effects of endotoxin. Immunochemically, R595 lipopolysaccharide is the innermost and more conserved part of endotoxin. Experimentally, antiserums against the R595 mutant have been reported to be protective in animal models.[14,15] Clinically, the level of IgG antibodies to the R595 mutant correlated with the outcomes of patients with gram-negative bacteremia.[16,17]

METHODS

Study Design

The goals of this study were to investigate whether standard intravenous immune globulin would be effective in preventing infection in high-risk postsurgical patients, to determine whether core-lipopolysaccharide intravenous immune globulin would reduce systemic infections due to gram-negative bacteria in these patients, and to compare the two agents. The study evaluated three agents: standard immune globulin, core-lipopolysaccharide immune globulin, and placebo. The incidences of acquired infections, episodes of systemic infection, and death were the primary outcome variables, and the length of stay in the ICU and in the hospital the secondary

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outcome variables. This was a multicenter, placebo-controlled, double-blind study, approved by the human-research committees of each participating center.

We assumed that the rate of systemic infection among the patients given placebo would be approximately 20 percent. Accordingly, we calculated that each of the three study groups should contain 130 patients to give the study a power of 90 percent to show a 50 percent reduction in the incidence of systemic infection in the core-lipopolysaccharide immune globulin group, with a 5 percent level of significance. A one-tailed significance level was used in calculating the size of the sample, since the goal of the study delineated at its inception was to demonstrate a significant positive effect of immune globulin prophylaxis; otherwise, this treatment would not be given in the future. However, two-tailed P values are reported throughout this report. A safety analysis was performed by an independent oversight committee upon the enrollment of every 90 to 100 patients.

Criteria for Eligibility

On the basis of postsurgical infection rates reported in a previous study of hyperimmune plasma containing the J5 antibody,[13] patients who had undergone one of the following seven types of surgery were eligible for the present study: esophageal surgery for cancer, contaminated abdominal operations (for example, surgery for abdominal abscesses, fistulas, or perforations), "second-look" abdominal operations after failure of a previous procedure, surgery for severe gastrointestinal hemorrhage requiring transfusion of more than 10 units of blood, peritoneal lavage for severe pancreatitis with more than three of the features described by Ranson et al.,[18] surgery for ruptured aortic aneurysms or aneurysms requiring transfusion of more than 20 units of blood, and surgery for severe abdominal or retroperitoneal trauma requiring more than 10 units of blood and tracheal intubation for more than 24 hours. Informed consent was obtained from each participant. All consenting patients more than 16 years old were enrolled if they had been admitted to the ICU within the preceding 36 hours and were expected to remain there at least 48 hours.

Patients were not eligible if they had clinical signs of a systemic infection at randomization (see definitions of infections, below). In addition, blood cultures were performed in every patient at entry, and all patients with bacteremia were excluded. Additional criteria for exclusion included evidence of shock, a decision not to provide optimal therapy, the likelihood of death within 48 hours, pregnancy, and previous randomization in the study or receipt of immune globulin during the three months before the study.

Randomization and Participating Centers

Randomization was performed by the pharmacists of the participating study centers according to computerized lists generated by a random-number program. The patients were balanced in equal blocks of six and stratified according to which of the seven types of surgery they had undergone; stratification was performed separately for each participating center. Each patient remained in the same study group throughout the trial.

The numbers of patients who were enrolled and could be evaluated at the seven participating study centers were as follows: Saint-Luc, Brussels, Belgium — 99 patients enrolled and 93 evaluated; Lausanne, Switzerland — 86 and 86, respectively; Basel, Switzerland — 52 and 51, respectively; Zürich, Switzerland — 48 and 46, respectively; Saint-Pierre, Brussels — 30 and 28, respectively; Geneva — 25 and 15, respectively; and Providence, Rhode Island — 12 and 10, respectively. The investigators at each center were blinded to the agents that the patients received.

Preparation and Dosage of Infusions

The standard intravenous immune globulin used (Gammagard, Baxter Healthcare, Hyland Division, Glendale, Calif.) is a sterile, lyophilized, highly purified preparation of immune globulin manufactured by the cold-ethanol process of Cohn and Onckley and further purified by ion-exchange chromatography. The IgG molecules do not undergo any chemical modification. It is prepared from pools of 10,000 to 30,000 units of plasma from paid donors at plasmapheresis centers.

Core-lipopolysaccharide intravenous immune globulin was prepared from plasma from 290 donors selected for their high titers of naturally occurring antibody to *S. minnesota* R595 lipopolysaccharide, as measured by enzyme-linked immunosorbent assay (ELISA). Donors in the top 10 percentiles of those screened were selected for this product. It was kept frozen as plasma or fraction II paste until sufficient quantities were collected for processing as described for the standard immune globulin.

The levels of anti-R595 lipopolysaccharide IgG antibody averaged 0.9 g per liter in the two lots of core-lipopolysaccharide immune globulin and 0.125 g per liter in the nine lots of standard immune globulin used in this study. Each immune globulin was given in a dose of 400 mg per kilogram of body weight, for a maximum of 30 g per infusion.

The placebo was 25 percent albumin in 500 ml of physiologic saline, given in a dose of 8 ml per kilogram. The volume was calculated to be equal to the volume of each immune globulin.

The hospital pharmacist at each institution reconstituted the test preparations and supplied the investigator with coded bags ready for infusion. Patients received the appropriate infusion on day 1 and every seven days until they were discharged from the ICU, for a maximum of four infusions. The initial rate of infusion was 0.5 ml per kilogram per hour, which was doubled every 20 minutes until a maximum of 4 ml per kilogram per hour was reached.

Measurement of IgG and Anti-R595 Lipopolysaccharid IgG Antibody

Blood samples were obtained for measurement of serum IgG before the first infusion of the study agent, and two hours, two days, and seven days later, before the next infusion. The samples were stored frozen at −70°C and analyzed after the study was completed. IgG was measured according to standard methods with a nephelometer (Behring, Marburg, Germany) (normal range in adults, 8.2 to 17 g per liter). Anti-R595 lipopolysaccharide IgG antibodies were measured by ELISA of serum from 10 patients per study group before the first infusion and two hours and two days later, as described elsewhere.[19] The results were expressed in ELISA units (optical-density value × serum dilution).

Data Collection

A complete history and a physical examination were performed in each patient. All patients were followed daily by an investigator at each center during their stay in the ICU and for 14 days after the last infusion. A coordinating investigator visited all participating centers every four to eight weeks, discussed all patients with the local investigator, and prepared flow charts for a computerized data base. In addition, all patients who died and all those with diagnostic problems or complicated clinical courses were discussed with a second investigator. At the end of the study, the code was broken only after the local investigator and consultants reached a consensus about each patient's eligibility and the nature of any episodes of infection.

Definitions of Infections

Focal infections present at randomization or acquired during the study were reported and defined according to standard criteria. Pneumonia was diagnosed if the patient had clinical features such as fever, cough, sputum, and rales and radiologic features such as new or worsening pulmonary infiltrates.[20] It was diagnosed microbiologically if cultures obtained with a protected brush during bronchoscopy were positive and if isolates from sputum culture contained a predominant organism and more than 25 polymorphonuclear cells and fewer than 10 epithelial cells per low-power field (×100) on microscopical examination.[21] Abdominal infection was defined by the presence of a purulent discharge and a positive culture. Urinary tract infection was defined by the presence of at least 10^5 bacterial colony-forming units per milliliter of urine.

An episode of systemic infection was defined as sudden clinical deterioration with evidence of infection, fever (temperature

>39°C), and at least one of the following: altered mentation, hypoxemia (partial pressure of arterial oxygen <70 mm Hg [9.3 kPa] while the patient was breathing room air), and elevated plasma lactate levels (>2 meq [mmol] per liter) or oliguria (<30 ml of urine per hour). Septic shock was indicated by a systolic blood pressure below 90 mm Hg or a decrease of more than 30 mm Hg in the blood pressure in conjunction with compatible clinical manifestations, in the absence of other causes of shock, such as hypovolemia, myocardial infarction, or pulmonary embolism, despite volume expansion and the administration of vasopressors in adequate amounts for more than one hour. If the hypotension could be reversed, a diagnosis of septic shock was accepted only if two of the following signs were present: sudden oliguria (<30 ml per hour), hypothermia (<36°C), hypoxemia (partial pressure of arterial oxygen <70 mm Hg [9.3 kPa] or a decrease of >25 percent of the previous value), metabolic acidosis (pH <7.3 or base excess below −10 mmol per liter), coagulation abnormalities (prothrombin time <50 percent, partial-thromboplastin time >40 seconds, or increase of fibrin split products >0.016 g per liter), thrombocytopenia ($<100\times10^9$ per liter or a decrease of 50 percent of the previous value), or sudden deterioration in mental status. Systemic episodes of infection and septic shock were attributed to a particular microorganism if it grew from a blood culture or from the site of a focal infection that was considered to be the source of the systemic episode. For a diagnosis of infection due to *Staphylococcus epidermidis*, viridans streptococci, diphtheroids, or bacillus species, two repeat blood cultures had to be positive.

All deaths occurring during hospitalization were recorded. Because of the complexity of the cases, the role of infection in death was not assessed.

Statistical Analysis

The comparability of the three study groups when the study began was determined with the use of parametric and nonparametric techniques, as appropriate. The chi-square test was used to evaluate qualitative data, and one-way analysis of variance to evaluate quantitative data. In all analyses, three-way comparisons were made initially; specific groups were compared only if these overall analyses showed significant differences.

The data on infection were assumed to have been obtained by three Poisson processes, one for each study agent. The incidences of infections were analyzed in pairwise fashion, with a large-sample normal approximation to the comparison of Poisson means,[22] to take into account the possibility of multiple infections in a single patient. Two-tailed P values were used as noted above. The method of Kaplan and Meier[23] was used to estimate the distribution of the times to the first focal infection in each study group, and the log-rank test for multiple groups was used to compare the distributions of survival times.[24] Because of large right-tail skews, the nonparametric Kruskal–Wallis test was used to compare the various measures of morbidity, such as the number of days of hospitalization and days in the ICU.[25] These data were summarized as medians and ranges.

Results

Safety Monitoring and Exclusions

From January 1987 to June 1989 (30 months), 352 patients were admitted to the study. There were 10 adverse events possibly associated with the infusions: fever in four patients, a transitory decrease in blood pressure in three, a rash in two, and an anaphylactic reaction in one. Three events occurred in the placebo group, five in the core-lipopolysaccharide immune globulin group, and two in the standard immune globulin group. One infusion of the standard immune globulin was associated with an anaphylactic reaction.

Twenty-one patients were excluded from the analysis for the following reasons: ineligibility (nine patients), the presence of bacteremia or shock at randomization (seven), withdrawal of consent (three), and a decision to stop all treatments a few hours after randomization (two). In addition, two patients were excluded because the infusion was discontinued — in one patient because of a fluid overload and in the other because of an anaphylactic reaction.

Characteristics at Randomization

A total of 329 patients could be evaluated. Their stratification according to type of surgery and their important characteristics at randomization are shown in Table 1. There were no significant differences between the three study groups in age, weight, APACHE II (Acute Physiology and Chronic Health Evaluation[26]) score, interval between entry to the ICU and the first infusion, sex ratio, number of patients with various types of surgery, severity and types of underlying illnesses, antibiotic treatment, or presence of focal infections at entry.

Serum IgG Levels and Anti-R595 Lipopolysaccharide IgG Antibody Levels

The numbers of infusions administered during the study period were similar in the three groups and averaged about 1.5 infusions per patient. Serum IgG levels were measured before the first infusion (in 285 patients) and two hours later (in 277), two days later (in 269 patients), and seven days later (in 253) (Fig. 1). Before infusion, the mean IgG levels were at the lower limit of normal and were similar in the three groups. Two hours after infusion, there was a twofold mean increase in the levels of the groups receiving standard and core-lipopolysaccharide immune globulin. The levels decreased steadily thereafter, until day 7. No significant difference was observed between the two immune globulin groups. In the placebo group, IgG levels did not change during the two hours after infusion, after which they increased steadily until day 7.

The serum levels of anti-R595 lipopolysaccharide IgG antibody were measured in 10 patients in each study group. Before infusion, the median level was 0 ELISA unit (range, 0 to 15) in the placebo group, 0 unit (range, 0 to 22) in the standard immune globulin group, and 0 unit (range, 0 to 25) in the core-lipopolysaccharide immune globulin group; after two hours, the levels were 0 unit (range, 0 to 12), 29 units (range, 17 to 45), and 92 units (range, 58 to 111), respectively ($P<0.001$). After two days, the levels were 0 unit (range, 0 to 13), 19 units (range, 10 to 38), and 54 units (range, 24 to 81), respectively ($P<0.001$).

Incidence of Focal Infections Acquired during the Study

After randomization, infection developed in 53 patients in the placebo group (47 percent), 50 in the core-lipopolysaccharide immune globulin group (46 percent), and 36 in the standard immune globulin group (33 percent). The incidence in the standard

Table 1. Characteristics of the Study Groups at Randomization.*

Characteristic	Placebo (N = 112)	C-LPS Immune Globulin (N = 108)	Standard Immune Globulin (N = 109)
		mean ±SD	
Age (yr)	56.8±16.7	57.6±14.6	54.9±17.9
Weight (kg)	69.1±15.9	69.4±12.6	67.8±15.6
APACHE II score (points)†	7.8±5.0	8.3±5.5	7.7±5.2
Interval between entry to ICU and first infusion (hr)	19.2±9.7	18.6±10.1	18.0±9.3
		no. of patients	
Sex (M/F)	80/32	78/30	78/31
Type of surgery			
Esophageal surgery	36	36	37
Contaminated abdominal surgery	33	31	27
Second-look laparotomy	17	14	20
Severe gastrointestinal hemorrhage	8	9	6
Severe pancreatitis	5	3	7
Ruptured aortic aneurysm	7	7	5
Severe abdominal trauma	6	8	7
Severity of preexisting illnesses			
Nonfatal	62	64	66
Ultimately fatal	38	39	37
Rapidly fatal	12	5	6
Most frequent preexisting illnesses			
Nonhematologic neoplasm	38	41	44
Alcoholism	18	20	21
Chronic obstructive pulmonary disease	16	12	13
Diabetes	10	7	4
Antibiotic treatment	108	108	109
Focal infections at entry (no. of foci)	46 (55)	43 (48)	48 (53)

*No significant difference was observed between the three groups in any of the characteristics. C-LPS denotes core lipopolysaccharide.

†Score determined by the Acute Physiology and Chronic Health Evaluation system.[26]

immune globulin group was 30 percent lower than that in either of the other two groups ($P = 0.06$ for comparison of all three groups; $P = 0.03$ for comparison of standard immune globulin and placebo groups). When the time from randomization to the first focal infection was analyzed with the Kaplan–Meier technique (Fig. 2), the reduced rate of infections in the standard immune globulin group was observed mainly after seven days ($P = 0.04$ for comparison of the three curves; $P = 0.03$ for the comparison of the curves for the placebo and standard immune globulin groups by the multigroup log-rank test). This suggests that standard immune globulin prevented mainly infections of late onset — i.e., infections not already incubating at the time of randomization.

The rate of acquired focal infections per 100 patient-days was also reduced in the standard immune globulin group as compared with the placebo group (2.79 vs. 3.84, $P = 0.08$ by Poisson test) (Table 2). In contrast, the rate in the core-lipopolysaccharide immune globulin group (3.61) was similar to that in the placebo group. Although no statistically significant differences were noted when the various sources of infections were analyzed separately, standard immune globulin reduced infections due to gram-negative bacteria the most ($P = 0.17$) and significantly reduced the incidence of pneumonia ($P = 0.04$), mainly by reducing the incidence of gram-negative pneumonia ($P = 0.02$). The difference was not statistically significant for the other sites of infections. When the incidence of infections was analyzed according to the type of surgery, the rate was found to be significantly reduced in the standard immune globulin group as compared with the placebo group in the category with the most patients (esophageal surgery; $P = 0.01$), and there was a trend toward reduction of infection in the two other categories with large numbers of patients (contaminated abdominal surgery and second-look laparotomy); however, the numbers of patients in each subgroup are small. The difference in these three categories in aggregate was significant ($P<0.01$). The numbers of acquired infections in the other categories of surgery were too small to allow the categories to be analyzed separately (Table 3).

Incidence of Episodes of Systemic Infection and Septi Shock

Forty-one episodes of systemic infection (i.e., sudden deterioration with fever), 25 of which fulfilled the criteria for septic shock, were observed in 38 patients (Table 4). In 27 cases, blood cultures were positive (for gram-negative bacteria in 13 cases, gram-positive bacteria in 9 cases, and fungi in 5 cases). No significant difference was found between the three study groups in the incidence of these episodes.

Mortality and Duration of Hospitalization

The hospital mortality in the study population was 17.3 percent (57 patients). The mortality in the standard immune globulin group (13.8 percent) was 30 percent lower than that in the placebo group (19.6 percent) and the core-lipopolysaccharide immune globulin group (18.5 percent). This difference was not statistically significant (Table 5).

Among the surviving patients, the length of stay

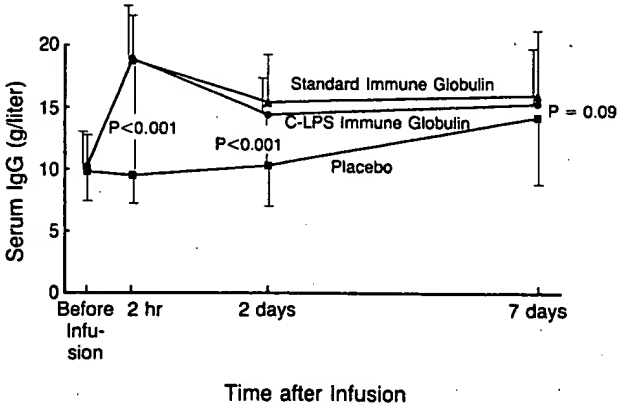

Figure 1. Serum IgG L v ls before and aft r Infusion of the Thre Study Agents.

The symbols represent means, and the T bars standard deviations. C-LPS denotes core lipopolysaccharide (circles).

in the ICU and the overall duration of hospitalization varied considerably. Approximately 15 percent of patients remained in the hospital for more than two months, usually for reasons unrelated to infection. Consequently, nonparametric tests were used for comparisons between groups. The length of stay in the ICU and total hospitalization were shorter in the standard immune globulin group than in the other two groups, by a median of 2.0 days and 7.5 days as compared with control values, respectively (Table 5). Furthermore, when patients who stayed more than 30 days in the ICU were excluded from the analysis to prevent skewing of the data by long hospitalizations, the differences became greater ($P = 0.02$ and $P = 0.07$ for comparison of the three groups; $P = 0.005$ and $P = 0.03$ for comparison of the placebo and standard immune globulin groups, respectively).

Discussion

The goal of the study was to investigate whether two preparations of intravenous immune globulin were effective in preventing infections in patients at high risk for them after surgery. We found that prophylactic administration of a standard immune globulin significantly reduced the incidence of infections among its recipients as compared with placebo recipients. The incidence of pneumonia was also significantly reduced, especially pneumonia due to gram-negative bacteria; this is a potentially important finding because nosocomial infections of the lower respiratory tract due to gram-negative bacteria have a high incidence and case-fatality rate in patients in the ICU.[27-29] This prophylactic effect on infections was associated with shorter stays in the ICU and hospital. Thus, the treatment might be cost effective because of savings in hospital costs that are associated with decreased lengths of stay. These findings are worthy of further investigation. The findings of other studies suggest that standard immune globulin is effective in preventing bacterial infections in immunocompromised patients[1,2] as well as in patients with multiple trauma treated in an ICU, who also appeared to benefit principally by a reduction in the incidence of pneumonia.[3]

Infections due to gram-negative bacteria are a major source of concern in patients admitted to the ICU, and lipopolysaccharide-mediated events are responsible in great part for the poor outcome of patients with these infections. In this study, a preparation of hyperimmune immune globulin specifically directed against lipopolysaccharide had no effect on the incidence of systemic infections, septic shock, or acquired focal infections, as compared with placebo. This apparent lack of efficacy of core-lipopolysaccharide immune globulin contrasted with the results of treatment with standard immune globulin. Both preparations were manufactured according to the same procedures for

Table 2. Focal Infections Acquired during the Study, According to Source and Site.

Type of Infection	Placebo (N = 112)	C-LPS Immune Globulin* (N = 108)	Standard Immune Globulin (N = 109)	P Value†
Total patient-days at risk →	*1903*	*1772*	*1793*	
	no. of episodes (rate/100 patient-days)			
All acquired infections	73 (3.84)	64 (3.61)	50 (2.79)	0.08
Source				
Gram-negative bacteria	30 (1.58)	36 (2.03)	19 (1.06)	
Gram-positive bacteria	12 (0.63)	5 (0.28)	7 (0.39)	
Mixed	11 (0.58)	6 (0.34)	9 (0.50)	
Yeasts	3 (0.16)	4 (0.23)	4 (0.22)	
Virus	1 (0.05)	2 (0.11)	1 (0.06)	
Unknown	16 (0.84)	11 (0.62)	10 (0.56)	
Site				
Lung (pneumonia)	30 (1.58)	25 (1.41)	15 (0.84)	0.04
Gram-negative bacteria	16 (0.84)	18 (1.02)	5 (0.28)	0.03
Abdomen	25 (1.31)	20 (1.13)	18 (1.00)	
Gram-negative bacteria	6 (0.32)	9 (0.51)	5 (0.28)	
Urinary tract	7 (0.37)	7 (0.40)	8 (0.45)	
Gram-negative bacteria	5 (0.26)	4 (0.23)	6 (0.33)	
Other	11 (0.58)	12 (0.68)	9 (0.50)	
Gram-negative bacteria	3 (0.16)	5 (0.28)	3 (0.17)	

*C-LPS denotes core lipopolysaccharide.

†The rates were compared by the Poisson test. In all statistical analyses, three-way comparisons were performed. Specific groups were compared only if these overall analyses showed significant differences. The P values shown above represent comparisons between the placebo and standard immune globulin groups. In all other statistical comparisons, P values were more than 0.10.

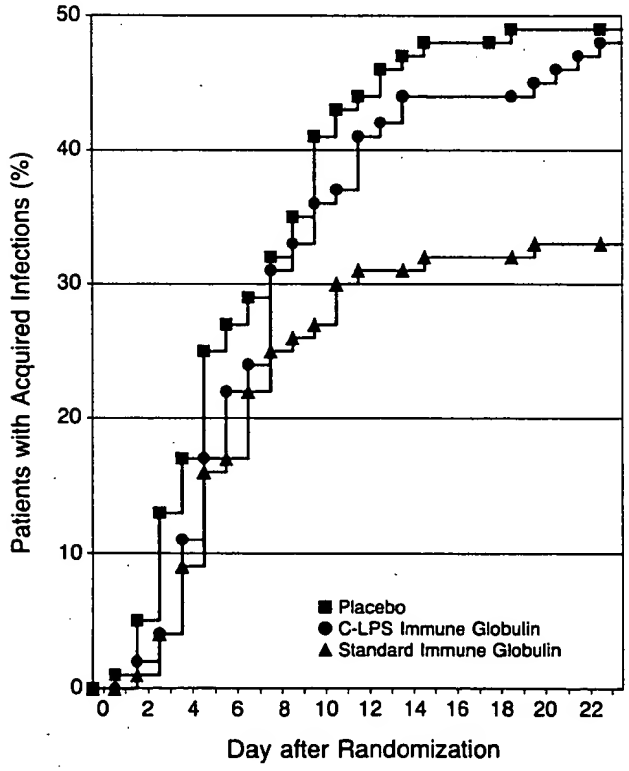

Figure 2. Interval between Randomization and First Focal Infection.

There was a significant difference between the three curves ($P = 0.04$) and between the curves for the placebo and standard immune globulin groups ($P = 0.03$). C-LPS denotes core lipopolysaccharide.

fractionation, but the fraction II paste of the core-lipopolysaccharide preparation was kept frozen until sufficient material was collected. This slight difference in the technique of preparation did not appear to affect the quality of the final product, since there was no detectable difference between the nine lots of standard immune globulin and the two lots of core-lipopolysaccharide immune globulin in anticomplement activity, the percentage of split products, C1q binding, or proportions of IgG subclasses. The binding of these lots to bacterial strains was found to be similar on ELISA (20 strains) and flow cytometry (4 strains). In addition, functional activity against four bacterial strains was checked through in vitro tests of opsonization and phagocytosis and in vivo protection experiments in mice, with similar results (data not shown). The clinical results suggest that the selection of donors on the basis of screening for IgG antibodies to R595 lipopolysaccharide may not be adequate for the selection of the protective antibodies that were present in the standard immune globulin. Ten thousand to 30,000 units of donated plasma were pooled to prepare each lot of standard immune globulin, but plasma from fewer than 300 donors was used to prepare the core-lipopolysaccharide product, which may have resulted in a narrower spectrum of antibodies. Alternatively, high titers of anti-R595 lipopolysaccharide antibodies in plasma might be associated with lower levels of antibodies to other determinants important for protection.

In finding that core-lipopolysaccharide immune globulin was ineffective, this study contrasts with previous studies of antiserum obtained from volunteers immunized with the rough mutant *E. coli* J5[12,13] and recent studies of two anti-lipid A IgM monoclonal antibodies,[30-32] which suggested that antibodies against core lipopolysaccharide might be protective against gram-negative infections. The core-lipopolysaccharide immune globulin used in the present study did not contain IgM, which has been considered necessary to afford protection against lipopolysaccharide,[33,34] although the data supporting this statement are controversial,[34] and IgG fractions obtained after immunization with *E. coli* J5 have been reported to protect rabbits from meningococcal endotoxin.[36]

It is possible that antibodies to R595 lipopolysaccharide do not protect against heterologous bacteria. In studies with antiserum to *E. coli* J5,[12,13] the mechanisms of protection remained unclear and could not be convincingly attributed to antibodies directed against J5 lipopolysaccharide, R595 lipopolysaccharide, or lipid A.[19,37] The protective power of antibodies to core lipopolysaccharide has not been unequivocally demonstrated; two other studies of J5 antiserum[38,39] and one of hyperimmune anti-J5 lipopolysaccharide immune globulin[9] have been unsuccessful. Studies with anti–lipid A monoclonal antibodies require confirmation.[40-42]

Table 3. Focal Infections Acquired during the Study, According to Type of Surgery.

Type of (Reason for) Surgery	Placebo (N = 112)	C-LPS Immune Globulin* (N = 108)	Standard Immune Globulin (N = 109)	P Value†
	no. of episodes (rate/100 patient-days)			
Esophageal surgery	24 (4.41)	18 (3.37)	9 (1.69)	0.01
Contaminated abdominal surgery	18 (3.31)	24 (4.61)	11 (2.50)	
Second-look laparotomy	13 (4.21)	4 (1.85)	8 (2.54)	0.07
Severe gastrointestinal hemorrhage	4 (2.65)	3 (2.38)	3 (3.30)	
Severe pancreatitis	4 (3.15)	4 (5.48)	8 (4.73)	
Ruptured aortic aneurysm	3 (3.16)	7 (4.55)	3 (2.68)	
Severe abdominal trauma	7 (5.26)	4 (2.68)	8 (5.93)	

*C-LPS denotes core lipopolysaccharide.

†The rates were compared by the Poisson test. In all statistical analyses, three-way comparisons were performed. Specific groups were compared only if these overall analyses showed significant differences. The P values shown above represent comparisons between the placebo and standard immune globulin groups. When the three types of surgery with the most patients (esophageal surgery, contaminated abdominal surgery, and second-look laparotomy) were analyzed in aggregate, the P value was less than 0.01.

Table 4. Episodes of Systemic Infection and Septic Shock Observed during the Study.*

	Placebo (N = 112)	C-LPS Immune Globulin (N = 108)	Standard Immune Globulin (N = 109)
Total patient-days at risk	*1903*	*1772*	*1793*
	no. of episodes (rate/100 patient-days)		
All systemic episodes			
All sources	12 (0.63)	14 (0.79)	15 (0.84)
Gram-negative bacteria	11 (0.58)	8 (0.45)	7 (0.39)
Gram-positive bacteria	1 (0.05)	4 (0.23)	4 (0.22)
Yeasts	0	2 (0.11)	3 (0.17)
Unknown	0	0	1 (0.06)
Septic shock			
All sources	6 (0.32)	10 (0.56)	9 (0.50)
Gram-negative bacteria	6 (0.32)	7 (0.40)	4 (0.22)
Gram-positive bacteria	0	2 (0.11)	3 (0.17)
Yeasts	0	1 (0.06)	1 (0.06)
Unknown	0	0	1 (0.06)

*No significant difference was observed between the three groups. C-LPS denotes core lipopolysaccharide.

Table 5. Mortality and Duration of Hospital Stay.

	Placebo	C-LPS Immune Globulin*	Standard Immune Globulin	P Value†
No. of deaths (%)	22 (19.6)	20 (18.5)	15 (13.8)	NS
No. of patients discharged alive from hospital	90	88	94	
Median no. of days in hospital (range)	29 (7–300)	24 (8–111)	21.5 (5–150)	0.06
No. of patients discharged alive from ICU	99	98	101	
Median no. of days in ICU (range)	6 (1–54)	5 (1–52)	4 (1–124)	0.02

*C-LPS denotes core lipopolysaccharide.

†NS denotes not significant. The P values shown represent comparisons between the placebo and standard immune globulin groups. The P values for the three groups were 0.14 (hospital stay) and 0.05 (ICU stay) (by nonparametric Kruskal–Wallis test).

We are indebted to the surgeons who allowed us to study their patients and to the pharmacists who prepared the infusions of immune globulin and placebo.

Appendix

The following are members of the Intravenous Immunoglobulin Collaborative Study Group: *Participating centers:* M. Reynaert, Hôpital Saint-Luc, Brussels; R. Chioléro, M. Bickle, G. Zanetti, and D. Heumann, Centre Hospitalier Universitaire Vaudois, Lausanne; C. Scheidegger, A. Widmer, and W. Zimmerli, Kantonsspital, Basel; J. Huber, C. Wolfisberg, M. Battegay, and R. Lüthy, Kantonsspital, Zürich; Y. Van Lathem, D. Weerts, and N. Clumeck, Hôpital Saint-Pierre, Brussels; P. Masouye, B. Miège, M.-C. Laverrière, and P. Suter, Hôpital Cantonal Universitaire, Geneva; and B.A. Veloudis, K.W. Burchard, and G. Peter, Rhode Island Hospital, Providence. *Safety committee:* A. MacCutchan, University Medical Center, San Diego, Calif.; S.H. Zinner, Rhode Island Hospital, Providence; and M.L. Lee, Baxter Healthcare Corporation, Glendale, Calif. *Baxter Healthcare collaborators:* S.G. Courter, D. Tait, and D.J. Rechtman.

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